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Original Research

Impaired seroconversion after SARS-CoV-2 mRNA vaccines in patients with solid tumours receiving anticancer treatment

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Abstract ***Background:*** Patients with solid tumours have high COVID-19 mortality. Limited and heterogeneous data are available regarding the immunogenicity of SARS-CoV-2 mRNA vaccines in this population.

Methods and findings: This is a prospective, single-centre cohort study aiming at evaluating seroconversion in terms of anti-spike antibodies in a population of patients with solid tumours undergoing cancer therapy within 2 months before the second vaccine dose, as compared with a cohort of controls. Subjects who were not SARS-CoV-2 naïve were excluded, and 171 patients were included in the final study population (150 vaccinated with BNT162b2, 87.7%; 21 with mRNA-1273, 12.3%) and compared with 2406 controls. The median follow-up time

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from the second dose of vaccination was 30 days (12–42; IQR: 26–34). Most patients had metastatic disease (138, 80.7%). Seroconversion rate was significantly lower in cancer patients than in controls (94.2% versus 99.8%, $p < 0.001$). At univariate logistic regression analysis, Odds ratio (OR) for seroconversion was also reduced in older individuals (>70 years). A multivariate logistic model confirmed cancer as the only significant variable in impairing seroconversion (OR 0.03, $p < 0.001$). In the cancer population, a multivariate analysis among clinical variables, including the type of cancer treatment, showed ECOG PS > 2 as the only one of impact (OR 0.07, $p = 0.012$).

Conclusions: There is a fraction of 6% of patients with solid tumours undergoing cancer treatment, mainly with poorer performance status, who fail to obtain seroconversion after SARS-CoV-2 mRNA vaccines. These patients should be considered for enhanced vaccination strategies and carefully monitored for SARS-CoV-2 infection during cancer treatment.

1. Introduction

The morbidity and mortality of coronavirus disease-19 (COVID-19) were found higher in cancer patients, not only as the result of older age and multiple comorbidities but also as an independent risk factor [1–3]. Considering those patients receiving anticancer treatment, only cytotoxic chemotherapy (ChT) appeared to increase the risk of death for severe COVID-19, while no safety concerns emerged for checkpoint inhibitor immunotherapy (IOT), targeted therapy (TT) or radiotherapy [4]. An explanation might rely on ChT-induced immunosuppression, albeit discordant results were found regarding seroconversion after SARS-CoV-2 exposure in cancer patients treated with ChT [5–7].

As no definitive cure has been established for COVID-19, disease prevention is the most effective way to contain new cases, and major medical societies fostered priority mass vaccination in this high-risk population [8–11]. As the spike-protein (S) retains a pivotal role in viral infection and pathogenesis of COVID-19, novel messenger ribonucleic acid (mRNA) vaccines (BNT162b2 by Pfizer/BioNTech and mRNA-1273 by Moderna) were found able to induce adequate anti-S response in healthy patients, obtaining more than 90% efficacy in preventing a severe course of COVID-19 [12,13]. Despite these promising results, cancer patients were mostly excluded from clinical trials, and their ability of seroconversion is now the main issue of a growing number of studies [14–27]. However, some of these studies assessed heterogeneous populations, including both solid tumours and haematological malignancies. This might impact on the results given the higher immunosuppressive status of the latter, secondary to the malignancy of the immune cells themselves and the greater myelotoxicity of the treatments employed. Further, some presented results of seroconversion only after one dose of vaccination, used miscellaneous mRNA and adenoviral vaccines, and did not contemplate a molecular or serological proof of previous SARS-CoV-2 infection. Finally, control with healthy individuals was provided only in a few and limited in numbers.

The goal of our study is to: (a) evaluate immunogenicity of SARS-CoV-2 mRNA vaccination in a population of patients with solid tumours undergoing cancer therapy as compared with a cohort of controls, as assessed by quantifying levels of anti-S antibodies and measuring neutralising activity of the receptor-binding domain-angiotensin-converting enzyme 2 (RBD-ACE2); (b) investigate the potential differential impact of the main categories of treatment (ChT, IOT, and TT) on seroconversion and neutralising activity.

To this aim, we designed SINFONIA-V, a mono-institutional prospective observational study carried out at a comprehensive cancer centre (Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy), comparing results with those of an extensive surveillance program performed in the same institution in healthcare workers [28].

2. Materials and methods

2.1. Study design and participants

This prospective, single-centre cohort study included adult patients (age >18 years) with a diagnosis of solid tumour, receiving two doses of SARS-CoV-2 mRNA vaccination, and able to provide written informed consent. All subjects received anticancer treatment within 2 months before the second vaccine dose. Blood drawing for testing seroconversion was required to be 12–42 days after the date of the second vaccine. Life expectancy longer than three months was mandatory.

Seroconversion was evaluated as the production of anti-S immunoglobulin G (IgG) after the completion of a vaccination course (two doses of BNT162b2 or mRNA-1273) and compared with a cohort of historical controls from a surveillance program led from December 2020 to February 2021 in healthcare workers at the same institution (RENAISSANCE trial) [28]. The neutralising activity of anti-S IgG antibodies was measured in the cohort of cancer patients to support the accuracy of immunogenicity. To avoid the confounding effect of a potential previous infection, we excluded those subjects with anti-nucleocapsid (N) IgG seropositivity for both cases and controls. Finally, we evaluated if immunogenicity was influenced by clinical variables, including the type of anticancer treatment received (ChT, IOT, and TT, including hormonal agents).

The study was approved by the local ethics committee Milano Area 3 (Italy), the national ethics committee for the evaluation of clinical trials regarding COVID-19 at Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani (Rome, Italy), and the Italian Medicines Agency AIFA (Agenzia Italiana del Farmaco). Ethical principles were respected as established by the Helsinki Declaration and the Good Clinical Practice guidelines. In no way did therapeutic changes take place secondary to the results of this study.

2.2. Procedures

From April 2021, cancer patients received SARS-CoV-2 mRNA vaccination according to the mass immunisation plan developed by the Italian Ministry of Health. From June to July 2021, patients who fulfilled the above-mentioned inclusion criteria were invited to participate in the study. A 10 mL venous blood sample was collected for each subject to measure anti-S and anti-N IgG titers. In any case, blood sampling was performed before antineoplastic treatment administration, if the latter was planned for the same day. Samples were stored at room temperature for at most 4 hours upon collection, then centrifuged. The resulting plasma was conserved at +4 °C until processing, which occurred within 3 days. Data from medical records were annotated for each subject as previously specified by GP, ML, DP on the REDCap platform [29]. All collected data were preserved anonymously and with respect to the patients' privacy.

2.3. Laboratory methods

Extensive methods are described elsewhere [23] and provided in the Supplementary Methods. Anti-S IgG antibodies titers were evaluated by the LIAISON® SARS-CoV-2 TrimericS IgG assay (DiaSorin S.p.A., Saluggia, Italy), presenting a superior cut-off of 2.080 binding arbitrary units (BAU) per mL. Seroconversion was defined as the result of anti-S IgG titer >33.8 BAU/mL, which represents the lower limit of detection of the method [30].

2.4. Sample size and statistical analysis

Assuming a 99.9% seroconversion rate (H_0) according to the preliminary analysis in healthy controls (RENAISSANCE trial [28]), and with at least 168 vaccinated fragile patients, we have 90% power to observe an

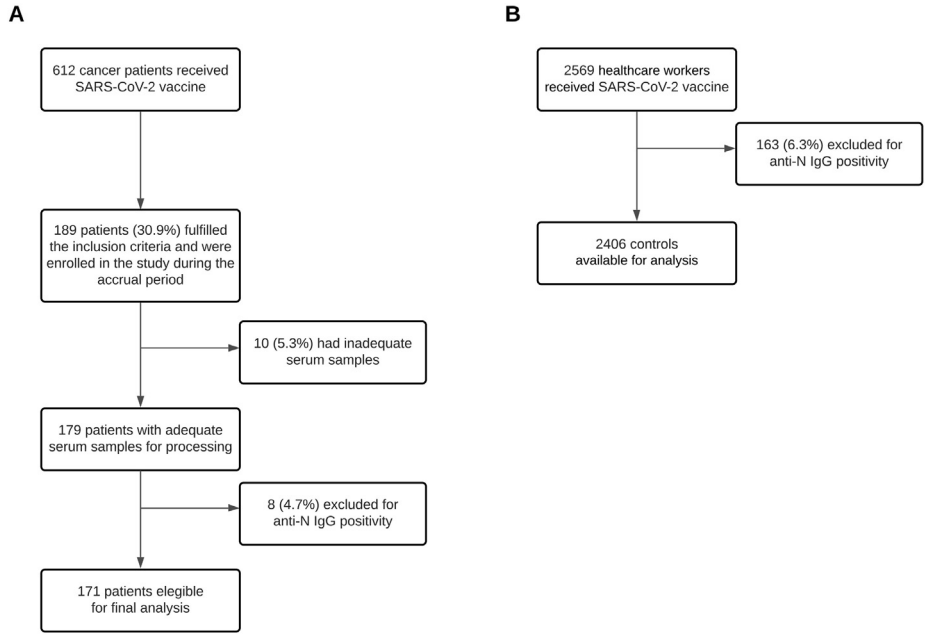

Fig. 1. **Consort diagram.** Flow diagram showing the selection process of cancer patients (**A**) and healthcare workers as control cohort (**B**). Keys: Anti-N IgG = anti-nucleocapsid immunoglobulin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 1
Characteristics and seroconversion of cancer patients and healthcare workers evaluated in the study.

	Patients with cancer (N = 171)	Healthy controls (N = 2406)	p
Median age, years [IQR]	68 [58–73]	48 [36–56]	<0.001
Age category			
<30	0.6% (1)	10.0% (241)	<0.001
30–39	3.5% (6)	21.6% (519)	
40–49	7.6% (13)	21.5% (517)	
50–59	16.4% (28)	33.3% (801)	
60–69	29.8% (51)	13.2% (318)	
≥70	42.1% (72)	0.4% (10)	
Sex			
Male	40.9% (70)	30.2% (726)	0.004
Female	59.1% (101)	69.8% (1680)	
Race			
Caucasian	97.7% (167)	NE	NA
Other	2.3% (4)		
Mean BMI, kg/m2 [IQR]	25 [22–28]	24 [21–27]	0.020
Smoking			
Active	24.6% (42)	NE	NA
Former	11.7% (20)		
Never	63.7% (109)		
mRNA vaccine	100% (171)	100% (2406)	
BNT162b2	87.7% (150)	100% (2406)	1.000
mRNA-1273	12.3% (21)	0% (0)	
ECOG PS			
0–1	83.0% (142)	NA	NA
2	13.5% (23)		
3	3.5% (6)		
Comorbidities			
No comorbidities	32.7% (56)	77.3%[a]	NA
At least one comorbidity	67.3% (115)	22.7%[a]	
Cancer histology			
Colorectal cancer	24.6% (42)	NA	NA
Breast cancer	21.1% (36)		
Non-small cell lung cancer	15.8% (27)		
Ovarian cancer	7.6% (13)		
Pancreatic cancer	7.0% (12)		
Stomach cancer	7.0% (12)		
Others	16.9% (29)		
Cancer stage			
Advanced/metastatic	80.7% (138)	NA	NA
Locally advanced	15.8% (27)		
Early	3.5% (6)		
Context of cancer treatment			
Palliative	83.0% (142)	NA	NA
Adjuvant	17.0% (29)		
Anticancer treatment			
ChT ± TT	62.0% (106)	NA	NA
IOT ± TT	11.1% (19)		
ChT + IOT	2.3% (4)		
TT alone	24.6% (42)		
Seroconversion			
No	5.8% (10)	0.02% (4)	<0.001
Yes	94.2% (161)	99.8% (2404)	

Keys. BMI = body mass index; ChT = cytotoxic chemotherapy; ECOG = Eastern Cooperative Oncology Group; IOT = immune checkpoint inhibitor immunotherapy; IQR = interquartile range; mRNA = messenger ribonucleic acid; N = numerosity; NA = not applicable; NE = not evaluated; PS = performance status; TT = targeted therapy.

[a] Data on comorbidities in the control group comes from a subset of 428 subjects from the RENAISSANCE study.

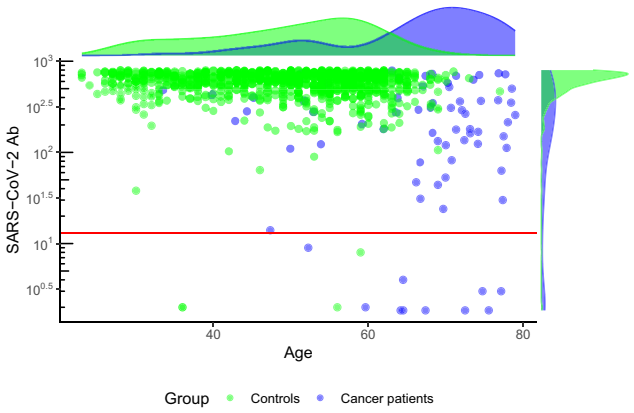

Fig. 2. **Distribution of anti-S antibody titer according to age in cancer and control cohorts**. The scatter plot displays anti-S Ab titer (y-axis, log scale) versus age (x-axis) in patients with titer under the essay upper limit of detection (2080 BAU/ml), with marginal density distribution on right and top, respectively; the red line shows the seroconversion limit (33.8 BAU/mL) of the essay. Keys: Ab = antibody; anti-S = anti-spike; BAU = binding arbitrary units; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

absolute reduction of 4% in seroconversion rate (H_1), with a clinical significant δ threshold of at least 1% reduction, and a type I error of 2.5%. Clinically relevant variables were correlated with seroconversion rate and reported with proper significance tests and in a univariate/multivariate logistic regression model.

Clinical variables were then summarised with descriptive statistics according to type (categorical/numerical) as number (N) and percentage (%) or mean/median and interquartile range (IQR). All analyses were carried out with R statistical software [31], and a complete list and version of packages is available in supplementary methods online.

3. Results

From April to June 2021, 612 patients with solid tumours received SARS-CoV-2 mRNA vaccination at Niguarda Cancer Center. Among these, from June to July 2021, 189 patients fulfilled the inclusion criteria of the study, 10 samples were inadequate for processing, and 8 patients were not SARS-CoV-2 naïve, leading to 171 patients being included as the final study population as compared to 2406 controls without cancer [28] (Fig. 1).

The median follow-up time from the second dose of vaccination to blood sampling was 30 days (range: 12–42; IQR: 26–34). Overall, 87.7% of patients were vaccinated with BNT162b2 (N = 150), while the others received mRNA-1273 (12.3%, N = 21). The main demographic and clinical characteristics of the study population and controls are reported in Table 1.

As expected, subjects in the control cohort were younger and with fewer comorbidities than cancer patients. No other major differences were observed apart from a higher prevalence of male subjects and minor BMI discrepancy. In the cancer population, patients were in good condition according to their Eastern Cooperative Oncology Group (ECOG) PS: 142 were PS 0–1 (83.0%), while only 23 and 6 were PS 2 (13.5%) and PS 3 (3.5%), respectively. The list of comorbidities is reported in Supplementary Table 1. Most patients had metastatic disease (80.7%, N = 138). Only 17.0% were receiving adjuvant treatment, hence cancer-free at the time of vaccination (N = 29). Cancer treatment consisted of ChT with or without TT (62.0%, N = 106), IOT with or without TT (11.1%, N = 19), ChT + IOT (2.3%, N = 4), and TT alone, including hormonal agents (24.60%, N = 42). Almost all patients (94.7%, N = 162) received their last anticancer treatment administration in the 15 days before or after the second vaccine dose.

Seroconversion rate was significantly different between the cancer population and controls (94.2% versus 99.8%, respectively, $p < 0.001$) (Table 1). At univariate logistic regression analysis, odds ratios (OR) for seroconversion were significantly reduced in patients with cancer (OR 0.03, $p < 0.001$) and in older individuals (>70 years, OR 0.08) (Fig. 2). A multivariate logistic model confirmed cancer as the only significant variable in impairing seroconversion (OR 0.04, $p < 0.001$) (Fig. 3).

In the cancer population, we did not find any correlation between seroconversion and age, gender, BMI, steroid therapy (≥10 mg of daily prednisone) or absolute lymphocyte count before vaccination. As far as steroid therapy is concerned, none of the patients received chronic treatment with more than 25 mg/day of prednisone or equivalents. Similarly, the primary

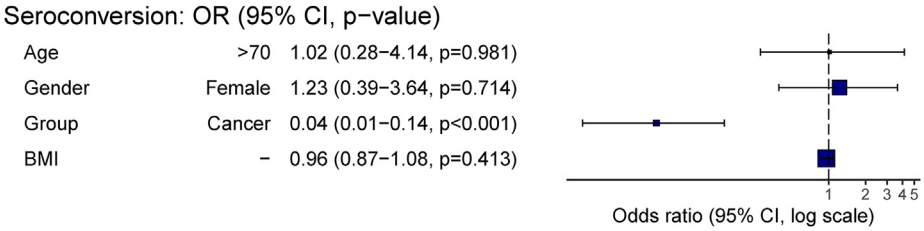

Fig. 3. **Multivariate analysis of clinical variables in the whole study population**. The forest plot shows odds ratios for seroconversion, according to age, BMI, gender and group (cancer versus control cohort). Keys: BMI = body mass index.

Table 2
Characteristics of cancer patients grouped according to seroconversion outcome.

	Not seroconverted (N = 10)	Seroconverted (N = 161)	p
Age (SD)	67.24 (7.88)	64.99 (11.62)	0.548
Gender, female (%)	5 (50.0)	96 (59.6)	0.788
BMI (SD)	27.27 (4.71)	69.45 (4.44)	0.132
Smoking history (%)			
Never	5 (50.0)	104 (64.6)	0.586
Active	3 (30.0)	39 (24.2)	
Former	2 (20.0)	18 (11.2)	
Steroid therapy (%)			
None	9 (90.0)	133 (82.6)	0.780
<10 mg of prednisone	1 (10.0)	23 (14.3)	
≥10 mg of prednisone	0 (0.0)	5 (3.1)	
ECOG PS (%)			
0–2	8 (80.0)	157 (97.5)	0.001
>2	2 (20.0)	4 (2.5)	
Lymphocytes before first dose/mm3 (SD)	1484.33 (441.81)	1728.05 (1118.82)	0.515
Lymphocytes before second dose/mm3 (SD)	1567.00 (535.46)	1691.61 (753.77)	0.608
Tumour primary (%)			
Colorectal cancer	3 (30.0)	39 (24.2)	1.000
Breast cancer	2 (20.0)	34 (21.1)	
Non-small cell lung cancer	3 (30.0)	24 (14.9)	
Ovarian cancer	0 (0.0)	13 (8.1)	
Pancreatic cancer	1 (10.0)	11 (6.8)	
Stomach cancer	1 (10.0)	11 (6.8)	
Others	0 (0.0)	29 (18.1)	
Stage (%)			
Locally advanced	2 (20.0)	31 (19.3)	0.782
Metastatic	8 (80.0)	130 (80.7)	
Context of cancer treatment, palliative (%)	8 (80.0)	134 (83.2)	1.000
Anticancer agents (%)			
ChT	8 (80.0)	102 (63.4)	0.468
IOT	1 (10.0)	22 (13.7)	1.000
TT	5 (50.0)	73 (45.3)	1.000
Neutralising Ab % (SD)	20.27% (14.28)	76.16% (24.64)	<0.001

Keys. Ab = antibodies; BMI = body mass index; ChT = cytotoxic chemotherapy; ECOG = Eastern Cooperative Oncology Group; IOT = immune checkpoint inhibitor immunotherapy; N = numerosity; NA = not applicable; PS = performance status; SD = standard deviation; TT = targeted therapy.
All continuous variables (age, BMI, lymphocytes before first and second dose, and neutralising antibodies) are reported as mean.

tumour site, staging and the type of anticancer treatment did not influence the probability of seroconversion. Among these characteristics, female gender and receiving IOT showed higher OR toward seroconversion in univariate analysis, but these findings were not statistically significant (OR 1.48 and 1.42, p = 0.550 and 0.743, respectively). In the multivariate analysis, ChT had the lowest probability of seroconversion among different kinds of treatment, without statistical significance (OR 0.18, p = 0.127). The only parameter significantly associated with reduced odds of seroconversion was ECOG PS > 2, with an OR of 0.10 (0.02–0.81, p = 0.015), as confirmed in the multivariate model, including also gender and type of anticancer therapy, with OR 0.07 (0.01–0.64, p = 0.012). The percentage of neutralising antibodies was consistent with seroconversion, displaying higher values in seroconverted patients (mean 76.2% versus 20.3%, p < 0.001). The characteristics of cancer patients grouped according to seroconversion outcome are reported in Table 2. Individual data of those patients lacking seroconversion are shown in Table 3. Results from the univariate and multivariate analysis are available in the Supplementary Tables 2 and 3

4. Discussion

We present the results of a prospective observational study investigating the immunogenicity of SARS-CoV-2 mRNA vaccination in patients with solid tumours undergoing anticancer treatment. In registration vaccine trials [12,13], this population was indeed absent and emerging data on limited cohorts suggest preserved safety but possible lower efficacy [14–16,20,21]. As compared with previous studies, we elected to assess a homogeneous population of patients with only solid tumours and all undergoing cancer treatment chronologically close to vaccination. Several previous studies also included patients with haematological malignancies who can present lower seroconversion rates because of more intense polychemotherapy and underlying immune system impairment itself.

Table 3
Characteristics of cancer patients lacking seroconversion after vaccination.

Patients	Age	Gender	BMI (kg/m2)	Smoking	Steroid therapy	Comorbidities	ECOG PS	Primary tumour	Stage	Cancer therapy	Therapy response	Days from therapy administration to 2nd dose vaccination	Days from vaccine to sampling	Neutralising activity (%)
1	68	Female	37	Former	No	Cardiovascular, respiratory	1	NSCLC	Locally advanced	Cisplatin + vinorelbine	NE	19	17	33.39
2	64	Male	23	Active	No	No	2	Stomach	Metastatic	FOLFIRI	SD	7	22	5.50
3	65	Female	27	Never	No	No	0	Breast	Locally advanced	Doxorubicin + cyclophosphamide	PR	22	24	29.23
4	77	Male	26	Never	No	No	3	Pancreatic	Metastatic	FOLFOX	PD	10	25	31.38
5	76	Female	24	Active	No	No	3	NSCLC	Metastatic	Pembrolizumab	PR	15	27	6.00
6	73	Female	24	Never	No	Endocrine, autoimmune	1	Breast	Metastatic	Everolimus + exemestane	SD	0	29	32.74
7	60	Male	26	Active	No	No	2	Colorectal	Metastatic	FOLFOX + panitumumab	PR	14	29	0.00
8	75	Female	28	Never	No	Cardiovascular, diabetes, endocrine	2	Colorectal	Metastatic	FOLFOX + panitumumab	PR	6	29	NE
9	65	Female	34	Never	No	Cardiovascular	1	Colorectal	Metastatic	FOLFOX + bevacizumab	PR	5	30	24.9
10	53	Male	23	Former	Yes	No	2	NSCLC	Metastatic	Carboplatin + pemetrexed	PR	36	37	NE

Keys: BAU = binding arbitrary units; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil, irinotecan, leucovorin; FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; mL = milliliter; NE = not evaluable; NSCLC = non-small cell lung cancer; PS = performance status; PD = progressive disease; PR = partial response; SD = stable disease.

In accordance with previous studies [14–16,20,21,26,27], our data in this specific population demonstrate a lower probability to obtain seroconversion after a complete course of SARS-CoV-2 mRNA vaccination. About 6% of cancer patients in treatment failed to develop an immune response after mRNA vaccination, as compared to only 0.2% in controls, accounting for a 30-fold higher probability. Of note, all 4 subjects with no antibodies in the control group were on immunosuppressive treatment with mycophenolate mofetil at the time of vaccination, impacting on seroconversion [28].

Among cancer patients, the only factor exerting a significant negative impact on seroconversion was the deterioration of clinical condition described as ECOG PS > 2. Despite the narrow number of patients in poor conditions (N = 6) in this study, the effect direction of ECOG PS on seroconversion impairment is unequivocal, and such finding is consistent with the clinical notion that patients in poor clinical conditions show a reduced immune response. We hypothesise that worse immunogenicity in these patients might be either secondary to higher underlying cancer disease burden leading to immune system exhaustion or to other concomitant medical conditions and comorbidities that could influence humoral response to vaccination [32–34]. Even though we were not powered to find a statistically significant association between seroconversion and different types of anticancer agents, 8 out of 10 patients not achieving seroconversion in our study were treated with chemotherapy, alone or in combination. The available evidence is inconsistent on this subject, with only a few trials showing such a negative association [15,17,19,22,23]. However, it should be considered that one of these trials also included haematological cancer patients treated with greater and B-cell specific immunosuppressive treatments [17]. In another study, only ChT + IOT, but not ChT alone, worsened the seroconversion rate [15]. Besides, we found no evidence that chronic steroid therapy hampers seroconversion, at least within the dosage and schedule of premedication to cancer treatment or for best supportive care [17]. Indeed, cancer patients in our study were receiving at most 25 mg of daily prednisone or equivalent and only time-limited higher doses as chemotherapy premedication.

Neutralising antibodies were also evaluated. In our study, the neutralising activity was significantly higher in seroconverted patients, confirming a positive correlation with seroconversion also in cancer patients.

Unlike other reports, our study focused on a population of patients undergoing active cancer treatment, as not only cancer but also its therapy is supposed to interfere with immune response [15,17,19,22,23]. We chose to evaluate full immunogenicity after a complete vaccination course, taking into consideration that the highest probability of seroconversion is reached 3–4 weeks after boosting and that the latter is now the standard of care [5,19,22]. We only investigated the immunogenicity of mRNA vaccines that were demonstrated to be the most effective in eliciting antibody response also in cancer patients [17]. Finally, all subjects with previous SARS-CoV-2 infection were excluded from the final analysis to avoid confusion bias [24,35–37].

The choice of such a specific population is both a strength and a limitation of our study. One limit is low numerosity (N = 171), especially of those patients receiving IOT (13.5%, N = 23), even though this cohort is one of the largest available at the moment [14,17,21,25]. Further, we could not distinguish the relative contribution of cancer itself from that of anticancer agents on seroconversion. In this regard, while seroconversion was proven to be independent of receiving treatment or not in one study, another reported higher seroconversion rates for cancer patients in clinical surveillance [17,20]. Another limitation of our study is that T cell response was not yet assessed, although it is planned. Besides, the humoral response is argued to play the main role in acquired immunity after vaccination, and it is thus, considered itself a surrogate of protection against SARS-CoV-2 [38]. Finally, we could not determine the distribution and mean of anti-S titer since the assay was capped at 800 AU/mL (2080 BAU/mL), and most results were over this upper limit (57.3% and 68.6%, in cancer and controls, respectively). On the other hand, to our knowledge, only one piece of evidence currently states that higher anti-S values provide improved protection from SARS-CoV-2; hence, the role of the median antibody titer in preventing infection is still debated [39] and might not necessarily detect a higher proportion of patients lacking seroconversion [17].

In conclusion, our study demonstrates a lower seroconversion rate in patients with solid tumours that received SARS-CoV-2 mRNA vaccines during anticancer therapy. A higher risk of lacking seroconversion was related to poor ECOG PS (> 2). No other factor significantly influenced immunogenicity, although few trends were observed according to the anticancer therapy type. Further studies and meta-analyses might clarify these results in the future. The 6% failure rate in seroconversion that we report is concerning in these fragile patients with higher morbidity and mortality from COVID-19 [40–43]. These patients should indeed be considered for enhanced vaccination strategies such as a third dose booster (repeated immune stimulation) and carefully monitored for SARS-CoV-2 infection during cancer treatment [44]. At present, we believe that facial masks and social distance are still warranted to safeguard fragile patients even if vaccinated and that these measures should be applied to their caregivers and healthcare workers. Besides, physicians should strongly encourage the immunisation of caregivers. The role of anti-S antibodies in clinical practice is still uncertain, as

precaution and additional preventive measures, such as third vaccine dose, are likely to be applied to the entire cancer population [45].

CRediT author statement

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.12.006.

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